(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/052892 A1

(51) International Patent Classification[7]: C07D 473/18, A61K 31/522, A61P 31/22

(21) International Application Number: PCT/EP2003/013951

(22) International Filing Date: 9 December 2003 (09.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02258456.9 9 December 2002 (09.12.2002) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: ANHYDROUS CRYSTALLINE FORM OF VALACYCLOVIR HYDROCHLORIDE

(57) Abstract: Valacyclovir hydrochloride in anhydrous crystalline form having substantially the following d-spacing pattern (in angstroms) (see (I)).

d-spacing
6.76
9.36
11.54
13.98
15.45
15.75
17.12
19.10
21.39
23.02
24.23
26.41
27.46
28.06

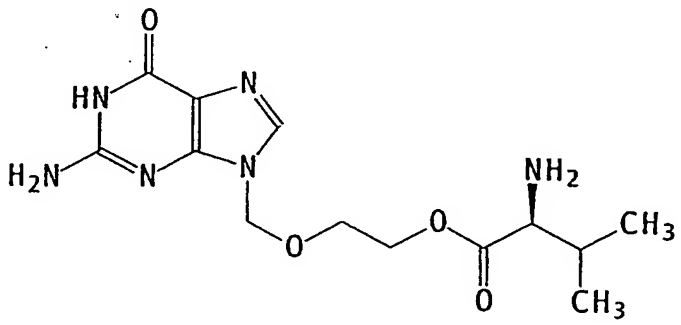
WO 2004/052892 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANHYDROUS CRYSTALLINE FORM OF VALACYCLOVIR HYDROCHLORIDE

The present invention relates to an anhydrous crystalline form of valacyclovir hydrochloride and to its uses and processes for the production thereof.

Valacyclovir is an L-valine ester with 9-[(2-hydroxyethoxy)methyl]guanine. It has the structure shown below



The preparation of valacyclovir is known and is described in, for example, US Patent No. 4957924 and its hydrochloride, which normally occurs as a hydrate, is now widely used as an antiviral agent, especially in the treatment of herpes viruses. Valacyclovir is a prodrug of acyclovir and hence has similar adverse effects, however, valacyclovir is a more bioavailable drug than its counterpart acyclovir and is absorbed more readily in the gastrointestinal tract following oral administration. Whilst valacyclovir hydrochloride is normally administered as a hydrate, it has been found to exist in other forms.

In US 6,107,302 an anhydrous crystalline form of valacyclovir hydrochloride is described which is prepared by contacting valacyclovir hydrochloride with 15 to 40% w/w of a lower alcohol or ketone. The resulting anhydrous crystalline valacyclovir

hydrochloride is characterised by its X-ray diffraction spectrum having characteristic d-spacing as follows: approximately 24.8, 10.25, 8.14, 7.31, 6.41, 5.85, 5.38, 5.24, 4.89, 4.43, 4.07, 3.71, 3.40, 3.31, 2.92 and 2.78 angstroms.

Hence, the hydrochloride form in US 6,107,302 has distinctive peaks at diffraction angles 2θ= approximately 8.62, 10.86, 12.12, 14.50 and 23.95°.

The present inventors have surprisingly found a new anhydrous crystalline form of valacyclovir hydrochloride which differs from those known in the prior art and which exhibits excellent stability both at room and elevated temperatures.

Hence, viewed from one aspect the invention provides valacyclovir hydrochloride in anhydrous crystalline form having substantially the following d-spacing pattern (in angstroms):

d-spacing
6.76
9.36
11.54
13.98
15.45
15.75
17.12
19.10
21.39
23.02
24.23
26.41
27.46
28.06

Viewed from another aspect the invention provides a

pharmaceutical composition comprising a valacyclovir hydrochloride form as hereinbefore described along with one or more pharmaceutical carriers/excipients.

Viewed from another aspect the invention provides a valacyclovir hydrochloride form as hereinbefore described for use in medicine, e.g. as an antiviral agent.

Viewed from a still yet further aspect the invention provides the use of a valacyclovir hydrochloride form as hereinbefore described in the manufacture of a medicament for use as an antiviral agent.

By anhydrous crystalline form according to the invention is meant a crystalline form having substantially the same X-ray powder diffraction pattern as hereinbefore described and shown in Figure 2. The valacyclovir hydrochloride form should be substantially free of any waters of hydration. The water content of the valacyclovir hydrochloride form of the invention should be below 1.5%, preferably below 1%, for example between 0.5% and 1%, e.g. 0.9% by weight. Water content can be measured using standard Karl-Fischer apparatus (e.g. as described in the 1990 US Pharmacopoeia at pages 1619-1621).

The infrared spectrum of the valacyclovir hydrochloride form of the invention should preferably be substantially as described below:

(the underlined peaks are considered the most characteristic of the anhydrous crystalline form of the invention)

IR (cm^{-1}): 3377.99, 3285.87, 3197.62, 2930.92, 1749.72, <u>1686.42</u>, 1631.12, 1607.17, <u>1572.60</u>, <u>1533.52</u>, 1476.48, 1364.98, 1298.63, 1258.79, 1248.27, 1225.22, 1132.81, 1097.06, 778.37, 759.33.

The person skilled in the art will appreciate that wavenumber measurements may vary slightly on different acquisitions or from machine to machine. Hence, the IR spectrum of the valacyclovir hydrochloride form of the invention should be substantially as described above, i.e. wavenumbers should be within 1% of the given values, preferably within 0.5% of the given values.

Thus, viewed from a further aspect the invention provides valacyclovir hydrochloride in anhydrous crystalline form having substantially the characteristic infrared peaks described above.

The X-ray diffraction pattern of the valacyclovir hydrochloride form may have substantially the following peaks (intensities may vary due to preferred orientation).

d-spacing	Rel. Int %
6.76	79.7
9.36	100.0
11.54	21.1
13.98	23.7
15.45	23.5
15.75	57.4
17.12	59.0
19.10	38.7
21.39	46.4
23.02	39.7
24.23	20.6
26.41	46.4
27.46	55.5
28.06	47.8

X-ray diffraction measurements should be taken using a standard Kα1 (Cu λ=1.5406 angstroms) radiation. Full details of the apparatus used may be found in the

experimental section.

The person skilled in the art will appreciate that d-spacing measurements may vary slightly on different acquisitions or from machine to machine. Hence, the d-spacing measurements of the valacyclovir hydrochloride form of the invention should be substantially as described above, i.e. d-spacing figures should be within 1% of the given values, preferably within 0.5 % of the given values.

The new anhydrous crystalline forms of the invention may be prepared from hydrated valacyclovir hydrochloride. Such a hydrate should be suspended in a lower alcohol, e.g. C_{1-6}-alcohol, preferably C_{1-4}-alcohol, especially ethanol which is substantially pure, i.e. substantially free of any other solvent or water. Preferably therefore, the solvent should be at least 99% lower alcohol, especially 99.8% lower alcohol, e.g. absolute ethanol.

The lower alcohol/hydrochloride mixture should then be heated at elevated temperature e.g. between 50-70°C, preferably 60°C for at least 12 hours, preferably 15-24 hours, e.g. 20-21 hours. The solvent may then be evaporated under reduced pressure, for example at 60°C and the crystalline solid thus obtained is valacyclovir hydrochloride as the new anhydrous crystalline form of the invention.

In an alternative embodiment the suspension of lower alcohol and valacyclovir hydrochloride in hydrated form may be added to refluxing lower alcohol, e.g. over 30 minutes. The refluxing alcohol should also be substantially pure as described above. Approximately one third of the solvent is then distilled off and the resulting suspension kept at room temperature, e.g. 20-25°C for at least 8 hours, e.g. 8-16 hours. The resulting solid may be filtered and washed with substantially pure lower alcohol, e.g. absolute ethanol and dried, e.g. under vacuum at 60°C. An anhydrous

crystalline form of valacyclovir hydrochloride of the invention is formed.

Once a seed crystal of valacyclovir hydrochloride in anhydrous crystalline form as claimed herein has been formed it is possible to produce more valacyclovir hydrochloride form of the invention using seeding techniques. For example, valacyclovir hydrochloride dihydrate can be suspended in substantially pure lower alcohol, e.g. isopropanol or isobutanol, and seeded with the anhydrous crystalline form. The suspension should be refluxed for a number of hours and filtered whilst still hot. After drying, the resulting solid is the anhydrous crystalline form of the invention.

Hence, viewed from a still yet further aspect the invention provides a process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form having the X-ray diffraction pattern as hereinbefore described comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and heating the resulting suspension;

2) evaporating the solvent under reduced pressure and isolating the resulting solid.

Alternatively, the invention provides a process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form having the X-ray diffraction pattern as hereinbefore described comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and adding the resulting suspension to substantially pure refluxing lower alcohol;

2) distilling off the solvent to form a suspension and maintaining the same at room temperature for at least 8 hours; and

3) isolating the resulting solid.

The valacyclovir hydrochloride forms of the invention exhibit remarkable stability and have been

shown to be stable at room temperature for over 3 years. Such stability is vital for a pharmaceutical since stocks thereof may be stored for long periods prior to use. Moreover, when heated at 100°C, the new form of valacyclovir hydrochloride exhibits stability for over 550 hours. The valacyclovir hydrochloride form of the invention therefore also shows surprising heat stability, again a property of critical importance to a pharmaceutical. The forms of the invention are therefore suitable for transport in countries where ambient temperatures are exceptionally high.

The valacyclovir hydrochloride form described above may be formulated and employed in medical treatment as is well known in the art. For example, valacyclovir hydrochloride may be employed as an antiviral agent especially in the treatment of diseases caused by various DNA viruses, such as herpes infections, for example, herpes simplex I and II, varicella zoster, cytomegalovirus, Epstein-Barr viruses or human herpes virus-6 as well as diseases caused by hepatitis B. The active compound can also be used for the treatment of papilloma or wart virus infections and may therefore be administered in combination with other therapeutic agents for example with zidovudine, to treat retroviral associated infections in particular HIV infection.

Pharmaceutical preparations may take the form of, *inter alia*, tablets, capsules, powders, solutions, suspensions or emulsions and they be formulated using standard techniques. While any administration route is possible the preferred route of administration is orally. The new valacyclovir hydrochloride form of the invention may be administered alone or in combination with other forms of valacyclovir hydrochloride or together with any other active ingredients. The amount of valacyclovir hydrochloride administered will vary depending on the patient but will be readily determined by the person skilled in the art. Dosage regimes are

known.

The invention will now be described further with reference to the following non-limiting examples and figures.

Figure 1 is the infrared spectrum of the valacyclovir hydrochloride form of the invention produced in Example 1;

Figure 2 is the X-ray diffraction spectrum of the valacyclovir hydrochloride form of the invention produced in Example 1.

Example 1

3g of valacyclovir hydrochloride (hydrated form) was suspended in 8 ml of ethanol 99.8% and heated at 60°C for 20-21 hours. The solvent was evaporated at 60°C under reduced pressure and the crystalline solid thus obtained was characterised as a new anhydrous crystalline form of valacyclovir hydrochloride.

Nicolet Avatar 320 (FT-IR)

IR (cm^{-1}): 3377.99, 3285.87, 3197.62, 2930.92, 1749.72, 1686.42, 1631.12, 1607.17, 1572.60, 1533.52, 1476.48, 1397.59, 1364.98, 1342.17, 1298.63, 1258.79, 1248.27, 1225.22, 1191.99, 1151.67, 1132.81, 1097.06, 1042.51, 1017.65, 868.28, 829.01, 778.37, 759.33, 729.45, 700.52, 688.32, 631.20.

XRD:

Diffractometer: PW1710 BASED
Tube Anode: Cu
Generator tension [kV]: 40
Generator current [mA]: 40
Wavelength alpha 1: 1.54060
Wavelength alpha 2: 1.54439
Intensity ratio alpha 2/alpha 1: 0.500
Divergence slit:1.5
Receiving slit: 0.2
Monochromator used: Yes

Start angle [0.52θ]: 5.000
End angle [0.52θ]: 60.000
Step [0.52θ]: 0.2
Maximum intensity: 1536.640
Time per step [s]: 1.000

Peak positions defined by: Minimum of 2nd derivative peak
Minimum peak tip width: 0.00
Maximum peak tip width: 1.00
Peak base width: 2.00
Minimum significance: 0.75
No. of peaks: 47

Data:

Angle [½2Õ]	d-value Á1 []	d-value Á2 []	Peak width [½2Õ]	Peak int [counts]	Back. int [counts]	Rel. int [%]	Signif
6.765	13.0556	13.0877	0.140	1225	98	79.7	10.2
8.160	10.8265	10.8532	0.200	61	81	4.0	1.5
9.360	9.4410	9.4643	0.140	1537	77	100.0	12.4
11.540	7.6620	7.6808	0.140	324	71	21.1	4.6
13.455	6.5755	6.5917	0.080	193	67	12.6	0.8
13.980	6.3297	6.3453	0.140	365	67	23.7	4.5
15.445	5.7325	5.7466	0.120	361	67	23.5	1.5
15.750	5.6221	5.6360	0.180	882	67	57.4	12.3
16.305	5.4320	5.4453	0.100	292	67	19.0	1.2
17.125	5.1737	5.1864	0.180	906	67	59.0	12.0
18.640	4.7565	4.7682	0.120	225	67	14.6	1.3
19.105	4.6417	4.6531	0.120	595	67	38.7	2.1
19.780	4.4848	4.4959	0.100	269	67	17.5	1.3
20.135	4.4065	4.4174	0.120	108	67	7.0	0.9
20.740	4.2793	4.2899	0.060	210	67	13.7	1.0
21.390	4.1508	4.1610	0.140	713	67	46.4	4.1
22.525	3.9441	3.9538	0.100	299	66	19.5	0.8
23.025	3.8596	3.8691	0.060	610	66	39.7	2.7
24.235	3.6695	3.6786	0.120	317	66	20.6	2.1
24.795	3.5879	3.5967	0.100	79	66	5.2	0.9
25.525	3.4869	3.4955	0.200	243	66	15.8	3.0
26.415	3.3714	3.3797	0.140	713	66	46.4	4.2
27.460	3.2455	3.2534	0.100	853	66	55.5	1.7
28.060	3.1774	3.1852	0.200	734	66	47.8	8.24
28.875	3.0896	3.0972	0.200	182	66	11.9	2.16
29.350	3.0406	3.0481	0.160	117	66	7.6	0.90
30.195	2.9574	2.9647	0.160	166	64	10.8	0.99
31.045	2.8784	2.8855	0.100	282	64	18.4	1.16
31.950	2.7989	2.8058	0.200	164	64	10.7	1.77
32.620	2.7429	2.7496	0.100	185	64	12.0	0.79
33.470	2.6752	2.6817	0.320	72	64	4.7	1.19
34.915	2.5677	2.5740	0.200	190	64	12.4	2.19
35.340	2.5378	2.5440	0.160	204	64	13.3	1.43
35.945	2.4964	2.5026	0.240	151	64	9.8	1.48
38.940	2.3110	2.3167	0.480	37	62	2.4	1.18
40.805	2.2096	2.2150	0.120	81	62	5.3	0.81
41.440	2.1772	2.1826	0.160	56	62	3.7	0.84
41.905	2.1541	2.1594	0.160	81	62	5.3	1.11
43.085	2.0978	2.1030	0.200	102	62	6.6	1.46
43.920	2.0599	2.0649	0.240	44	62	2.8	0.77
46.115	1.9668	1.9716	0.240	41	62	2.7	1.09
48.055	1.8918	1.8965	0.240	29	61	1.9	0.87
48.895	1.8613	1.8658	0.400	28	61	1.8	0.78
51.665	1.7678	1.7721	0.640	21	61	1.4	0.93
53.715	1.7051	1.7093	0.240	22	61	1.4	1.02
54.800	1.6738	1.6780	0.320	21	61	1.4	0.86
56.740	1.6211	1.6251	0.480	12	59	0.8	1.25

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Example 2

Valacyclovir hydrochloride (hydrated form) was suspended in ethanol 99.8%. The suspension was added over about 30 minutes to refluxing ethanol 99.8%. The solvent was distilled off and the suspension kept at 20-25°c for 12 hours. The solid was filtered, washed twice with absolute ethanol and dried under vacuum at 60°C. The crystalline solid thus obtained was characterised as a new anhydrous crystalline form of valacyclovir hydrochloride.

Example 3

10g of valacyclovir hydrochloride dihydrate (KF 6%) was suspended in 100 ml of isopropanol 99% and seeded with 50 mg of anhydrous crystalline valacyclovir hydrochloride. The suspension was refluxed for 5 hours and filtered hot. The solid was dried at 110°C for 10 hours (yield = 7.52g).

Example 4

10g of valacyclovir hydrochloride dihydrate (KF 6%) was suspended in 100 ml of isobutanol 99% and seeded with 50 mg of anhydrous crystalline valacyclovir hydrochloride. The suspension was refluxed for 5 hours and filtered hot. The solid was dried at 110°C for 10 hours (yield = 8.24g).

Claims

1. Valacyclovir hydrochloride in anhydrous crystalline form having substantially the following d-spacing pattern (in angstroms):

d-spacing
6.76
9.36
11.54
13.98
15.45
15.75
17.12
19.10
21.39
23.02
24.23
26.41
27.46
28.06

2. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 having substantially the X-ray diffraction pattern of Figure 2.

3. Valacyclovir hydrochloride in anhydrous crystalline form having substantially the characteristic infrared peaks

IR (cm^{-1}): 1686.42, 1572.60, 1533.52.

4. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 3 having substantially the characteristic infrared peaks

IR (cm^{-1}): 3377.99, 3285.87, 3197.62, 2930.92, 1749.72, 1686.42, 1631.12, 1607.17, 1572.60, 1533.52, 1476.48, 1364.98, 1298.63, 1258.79, 1248.27, 1225.22, 1132.81, 1097.06, 778.37, 759.33.

5. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 3 having substantially the infra-red absorption spectrum of Figure 1.

6. A pharmaceutical composition comprising a valacyclovir hydrochloride form as claimed in claim 1 to 5 along with one or more pharmaceutical carriers/ excipients.

7. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 for use in medicine.

8. Use of valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 in the manufacture of a medicament for use as an antiviral agent.

9. A process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and heating the resulting suspension;

2) evaporating the solvent under reduced pressure and isolating the resulting solid.

10. The process of claim 9 wherein said solvent is ethanol.

11. The process of claim 9 or 10 wherein the suspension is heated at between 50 to 70°C for at least 12 hours.

12. The process of claim 11 wherein the suspension is heated at 60°C for 20-21 hours.

13. A process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and adding the resulting suspension to substantially pure refluxing lower alcohol;

2) distilling off the solvent to form a suspension and maintaining the same at room temperature for at least 8 hours; and

3) isolating the resulting solid.

14. The process of claim 13 wherein the solvent and refluxing lower alcohol are ethanol.

15. The process of claim 13 or 14 wherein approximately one third of the solvent is distilled off to form said suspension.

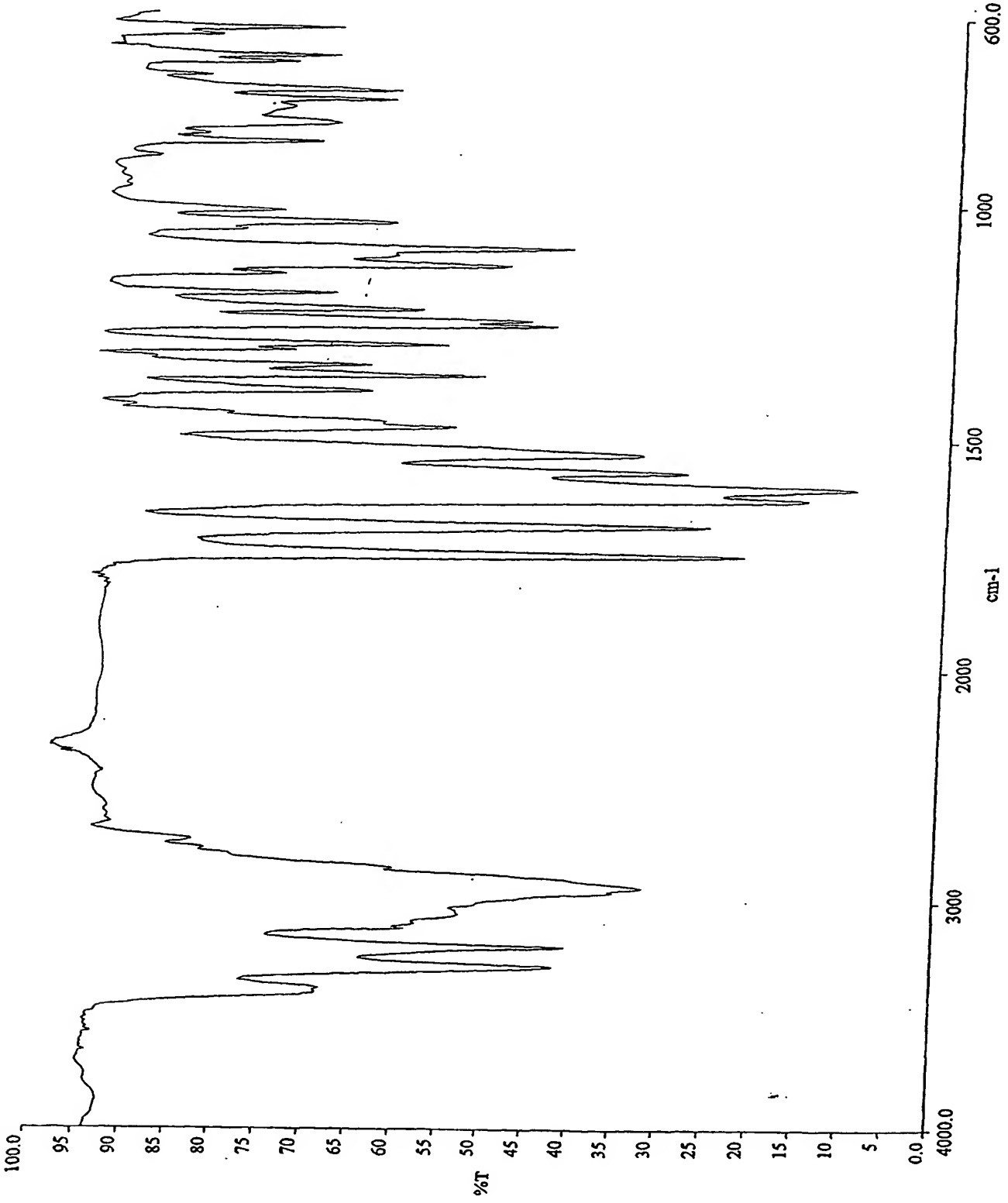
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Figure 1

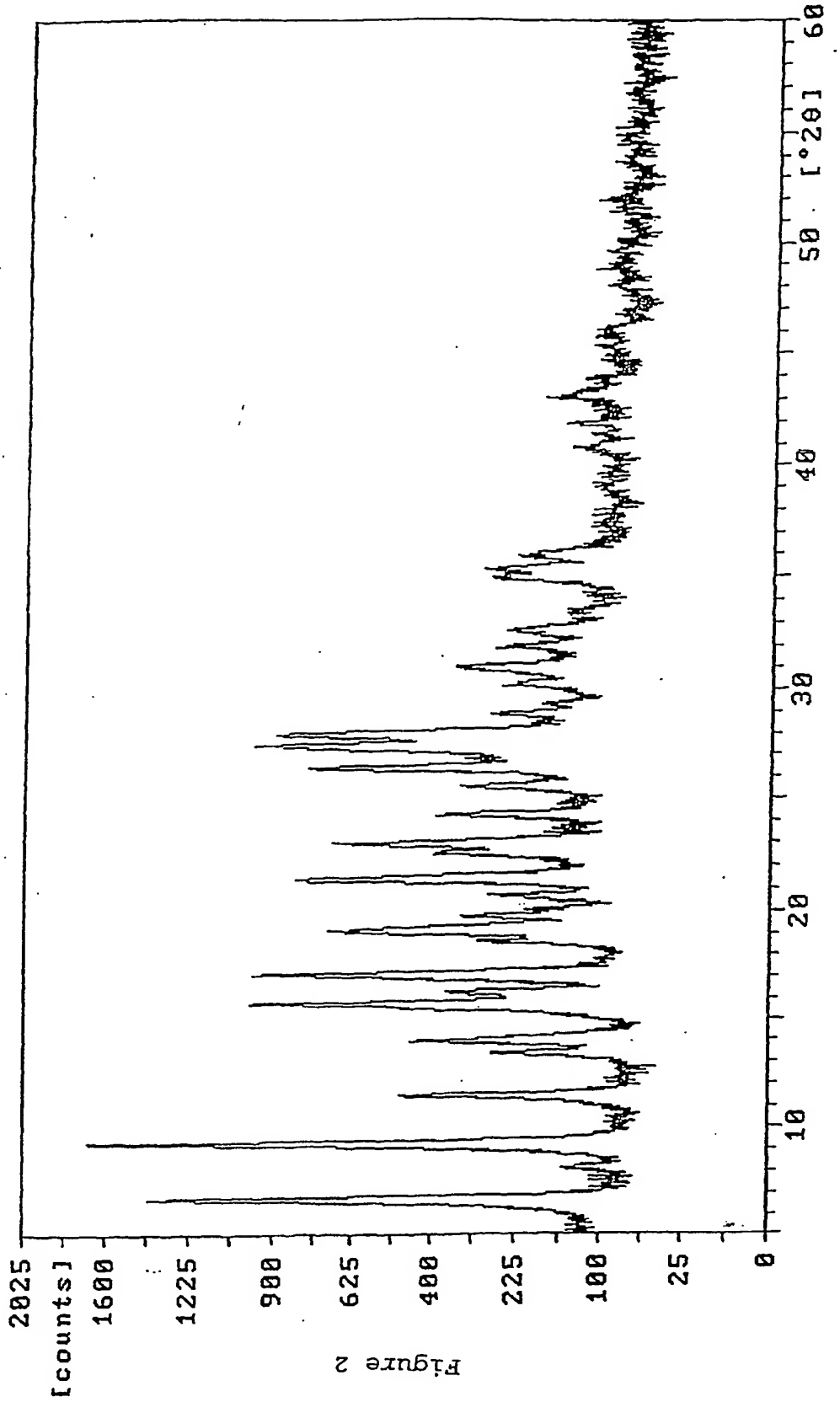

Figure 2